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Using Ultrasound

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Introduction

Historically, about 20% of head injuries sustained in combat have been non-penetrating (1). With better protective equipment and increased use of armored vehicles on the battlefield, the relative frequency of severe non-penetrating head injuries will likely increase. Prevention of secondary brain injuries following head trauma can be accomplished most easily when intracranial pressure (ICP) is monitored. However, current measurement techniques are invasive and thus not practical in the combat environment. The Pulsed Phase Lock Loop (PPLL) device, which was developed and patented by collaborators Dr. Yost and Dr. Cantrell, uses a unique, noninvasive ultrasonic phase comparison method to measure slight changes in cranial volume which occur with changes in ICP. The clinical application of such an instrument has significant challenges and the following studies were designed to characterize, validate, and modify the equipment and measurement procedures. Experiments were performed in-vitro to simulate the clinical environment, in cadavers to understand further the clinical considerations, and in-vivo to initiate clinical applications. The steps provide an important foundation for the development of a compact, noninvasive device for monitoring changes in intracranial distance. Clinical application may aid in the early detection of elevated ICP, decreasing risk of secondary brain injury and infection, and improved assessment of head-injured patients for additional medical evaluation or their ability to return to duty.

Year 01

Overview

We improved the pulsed phase-locked loop (PPLL) hardware by integrating software modifications such that our clinical studies will be greatly facilitated. Although mean ICP is commonly used for ICP monitoring, the analysis of ICP waveforms is also important because the waveforms contain information on intracranial compliance and cerebrovascular tonus which cannot be estimated from mean ICP (2). Our noninvasive technique is based upon detecting skull movements which occur with fluctuations in ICP. Although the skull is often assumed to be a rigid container with a constant volume, many researchers (3-7) have demonstrated that the skull moves on the order of a few μm in association with changes in ICP. These studies were designed to validate our noninvasive technique for the measurement of ICP waveforms.

Instrumentation Description

The ultrasound technique we utilized to detect skull pulsation is based upon a modification of the PPLL design (8), making it possible to measure slight changes in distance between an ultrasound transducer and a reflecting target. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer

(Figure 1). The instrument compares the phase of emitted and received waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 msec to 20 msec. The details of PPLL are described elsewhere (8, 9). Briefly, if path length is changed by Δx , the frequency shift (Δf) of the ultrasound which is made to maintain the 90° phase difference between the output of the device and the received signal can be expressed as $\Delta x/x = -\Delta f/f$ (see Appendix).

In order to provide continuous monitoring, we modified the PPLL circuit to integrate error signals of the phase shift from normal 90° phase difference (PPLL output). Theoretically, integration of the error signals also correlates with altered path length (Δx).

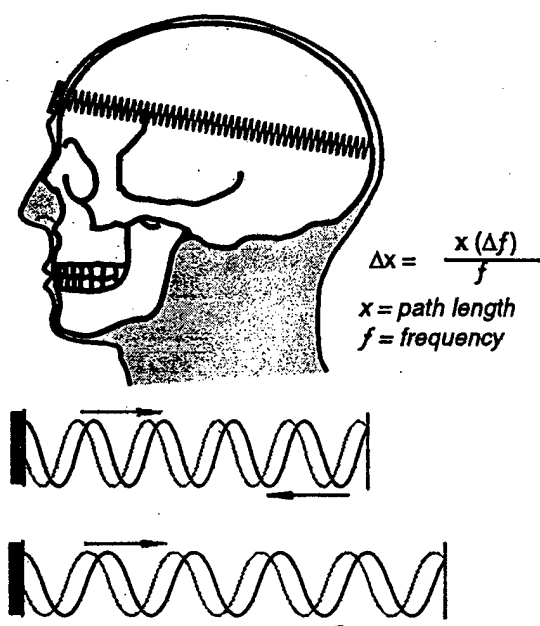


Figure 1 – Schematic illustration of the noninvasive pulse phase lock loop ultrasound device used to measure transcranial distance. Changes in pathlength induce changes in the frequency of the received acoustic wave. The PPLL frequency change induces a voltage output which is measured by the instrumentation and associated equipment.

In-vitro Testing

A specially constructed aluminum cylinder was used to examine the PPLL output characteristics. Two pressure-resistant tubes were connected to the cylinder filled with saline. The other ends of the two tubes were connected to a plastic syringe and a fiber-optic, transducer-tipped catheter (Camino Laboratories, San Diego) which measures fluid pressure, respectively. An ultrasonic transducer was placed on the top of the cylinder. Pressure pulsations were generated at a frequency of 1 Hz by pumping the syringe while

its amplitudes were changed randomly. Changes in distance were calculated from changes in ultrasound frequency.

Our model experiments demonstrated that changes in the PPLL output correlated with changes in the distance to a high degree (Figure 2). The relationship between the PPLL and displacement can be expressed by:

$$y = 2.33 \cdot 10^{-4} x + 0.0011 \quad \text{equation 1}$$

where x = distance (μm) and y = PPLL amplitude (voltage).

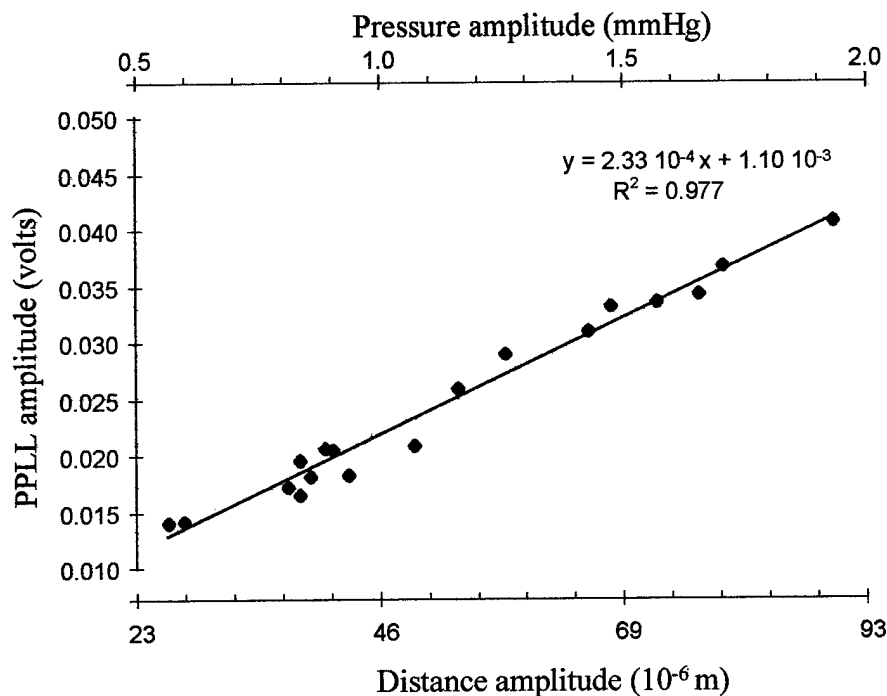


Figure 2 - The relation of the PPLL output to the pressure inside the cylinder and the distance between the transducer and the bottom of the tank, where x = distance (μm) and y = PPLL output (voltage).

Cadaver Experiments

These studies were designed to evaluate the correlation of PPLL output and directly-measured ICP in fresh human cadavera. A catheter was inserted into the frontal horn of the right lateral ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate the PPLL output with ICP directly, a fiber-optic, transducer-tipped catheter was placed in the epidural space through another burr hole. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. The experiment was performed using two different temperatures of saline (4°C and 20°C) to evaluate temperature dependence.

The PPLL output closely followed the pulsatile component of ICP (Figure 3). The results of fast Fourier transformation are provided in the top insert, showing the correlation between the PPLL output and ICP pulse cycles. The relationship between the PPLL and ICP amplitudes was expressed as the same equation in both saline temperatures:

$$y = 3.0 \cdot 10^{-4} x + 0.0011$$

equation 2

where x = ICP amplitude (mmHg) and y = PPLL amplitude (voltage).

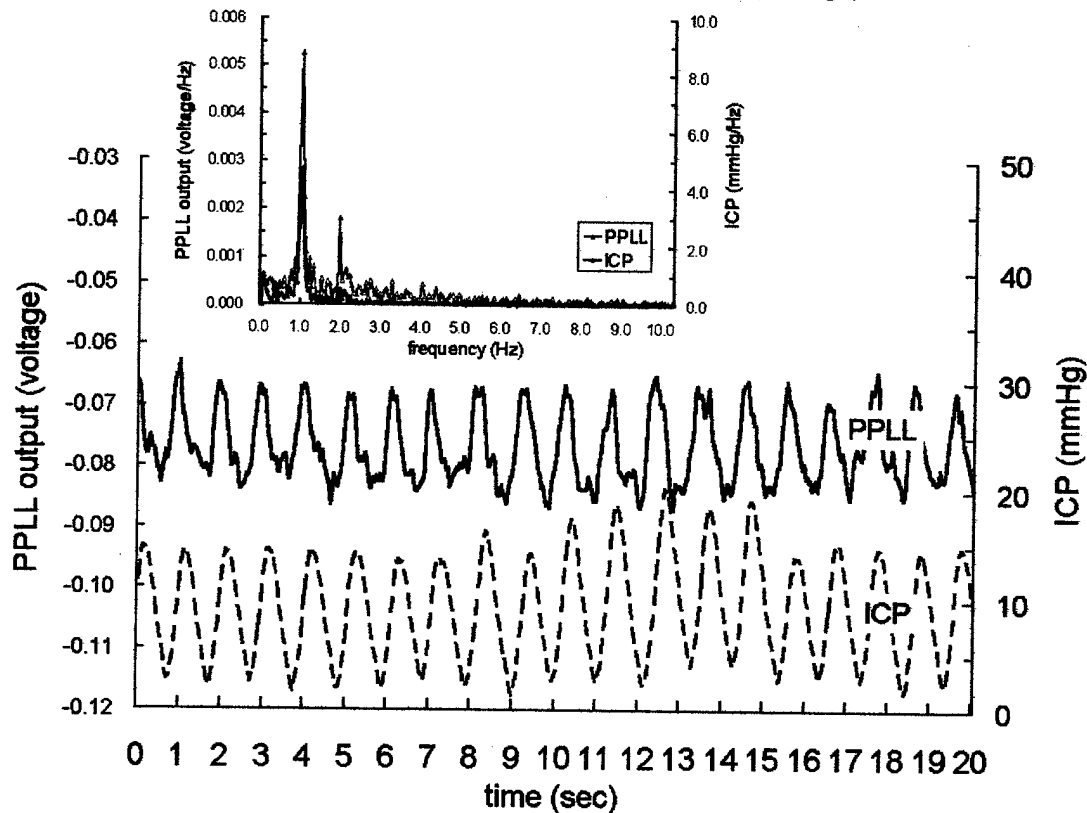


Figure 3 - Typical waveforms in the PPLL output and directly measured ICP are shown as solid and dash lines, respectively. The results of frequency analysis (fast Fourier transformation) are provided in the top insert.

These results demonstrate that our PPLL device can clearly detect changes in the integrated phase shifts of the transmitted ultrasound (PPLL outputs) in association with alterations in ICP. As shown in the Appendix, the observed phase shift can be caused by changes in the distance between the transducer and the opposite side of the skull and also by changes in the ultrasound velocity in the cranium. Infusion of saline into the ventricle could change the temperature inside the cranium, resulting in altered sound velocity. As another possible factor, changes in the density of the brain tissue due to altered ICP could affect ultrasound velocity. In the cadaver study, however, no significant difference was observed in the amplitudes of PPLL when different temperature saline was infused into the ventricle. Also, the cadaver model allows controlled ICP changes without the potential

confounding effect of cutaneous shifts of blood with posture in normal volunteers. Therefore, we believe that changes in the PPLL output observed in our cadaver studies represent small but detectable skull movements associated with alterations in ICP.

According to the equation 2, the ratio of PPLL amplitude to ICP amplitude is expressed as:

$$\Delta_{\text{int}} / \Delta \text{ICP} = 3.0 \cdot 10^{-4} \text{ (voltage / mmHg)} \quad \text{equation 3}$$

Using equations 1 and 3, the skull elasticity, defined as $\Delta \text{ICP} / \Delta x$, is approximately 1.6 mmHg / μm . Heisey and Adams (4) demonstrated that skull elastance in adult cats is 4.5 mmHg / μm by invasively measuring the skull movement across the sagittal suture with strain gauge. The difference between our data and theirs might be due to the difference in skull elasticity between cat and human. Also, we measured skull movements transversely, while they measured the movement only across the sagittal suture. This difference in the site of measurement may affect changes in the distance obtained.

This technique allows analysis of ICP waveforms noninvasively and will be helpful for understanding intracranial compliance and cerebrovascular tonus in general clinical settings and may be the first demonstration that it is possible to measure skull movements noninvasively in association with alterations in ICP.

Preparation for in-vivo studies

We received approvals for our clinical study protocols from the IRBs at US Army, NASA Ames Research Center, and Stanford University. Similar protocols are under review now at UCSD where most future studies will be undertaken.

Year 02

Overview

These studies were designed to continue validation of our noninvasive technique for the measurement of ICP waveforms. We analyzed ICP waveforms because these waveforms contain information on intracranial compliance and cerebrovascular tonus which cannot be estimated from mean ICP (2). Cadaver studies were continued with measurements performed during external compression of cadaver skulls. During this period we also undertook head-up and head-down tilt studies of normal volunteers after obtaining informed, written consent. We decided to study compression of cadaver skulls because ICP conditions could be more carefully controlled than in normal volunteers whose skin blood flow confounds data interpretation. Tilting experiments induce gravity-driven blood and fluid shifts which may induce measurable changes in cranial oscillations.

Instrumentation improvements

Although the ultrasonic frequency is altered every 0.5 ms by the PPLL circuit, the number of the ultrasonic frequency can be transferred to a recording system 3-5 times per second. This sampling rate is inadequate to analyze pulsatile components associated with a cardiac cycle. Recently, we modified a PPLL circuit to record pulsatile components of the cranial distance in higher sampling rates. The modified PPLL circuit integrates error signals of the phase shift from normal 90° phase difference while the ultrasonic frequency is being altered. The integrated error signal, which is obtained in the units of voltages, theoretically correlates with altered path length relatively.

We also performed signal averaging using the QRS complex of the electrocardiogram as a trigger. A data stream recorded over 30 seconds is fragmented using the QRS complex. Then, the fragmented data are simply summed up and divided by the number of a cardiac cycle. Although the length of each fragmented data is different from data to data due to the variability of a cardiac cycle, this variability is not taken into account. By averaging data across several cardiac cycles using the QRS complex, superimposed noises which are not associated with a cardiac cycle are canceled, and waveforms associated with arterial pulsation are analyzed more clearly.

Cadaver skull compression study

In supine position, a catheter was inserted into the frontal horn of the right ventricle through a burr hole, and the other end of the catheter was connected to pressure tubing and a plastic syringe. To correlate PPLL output with ICP directly, a fiber optic, transducer-tipped catheter was placed in the epidural space through another burr hole. The PPLL ultrasound transducer was placed on the temporal area above the ear and fixed with pressure cuff around the head to adjust the surface pressure on the transducer. Pulsatile changes in ICP were generated by infusing saline into the lateral ventricle at a frequency of 1 Hz. We recorded PPLL output while generating ICP pulsations and thereafter increased the circumferential pressure around the head in steps of 10 mmHg (0-40 mmHg) by inflating the pressure cuff. The PPLL output closely followed the pulsatile component of ICP. The ratio of PPLL amplitude significantly decreased along with increased external compression around the head (Figure 4).

$$y = -1.0 \cdot 10^{-5}x + 0.0008, R^2=0.87 (p=0.020) \quad \text{equation 4}$$

where x = circumferential compression (mmHg) and y = ratio of PPLL amplitude to ICP amplitude (voltage/mmHg).

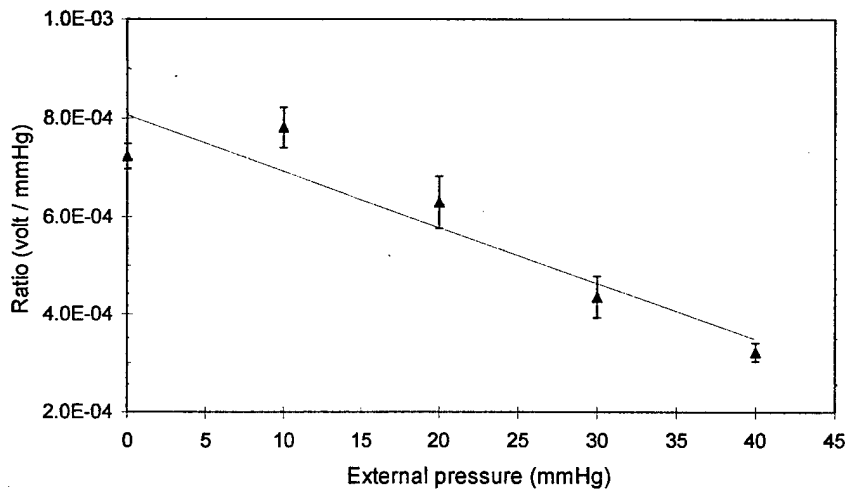


Figure 4 - External compression of cadaver skull reduces PPLL waveform amplitude, indicating that our noninvasive ICP technique detects pulsatile movements of bone and not skin vasculature.

Whole-body tilt study

This study was designed to investigate whole body tilting effects on ICP dynamics. We hypothesized that head-down tilt would elevate ICP due to blood shifts to the head. These studies were initiated following approval of the protocol by the IRB at UCSD.

Six healthy volunteers participated in this study, after giving informed written consent. To minimize accumulative effects caused by tilting, the subjects were randomly tilted up or down sequentially at 60°, 30° head-up, supine (0°), and 15° head-down position for one minute at each angle. Arterial blood pressure and heart rate were monitored with an inflatable wrap-on finger pressure cuff (Finapres Model 2300, Ohmeda, Englewood, CO)(10,11). The cuff pressure followed intra-arterial pressure changes continuously.

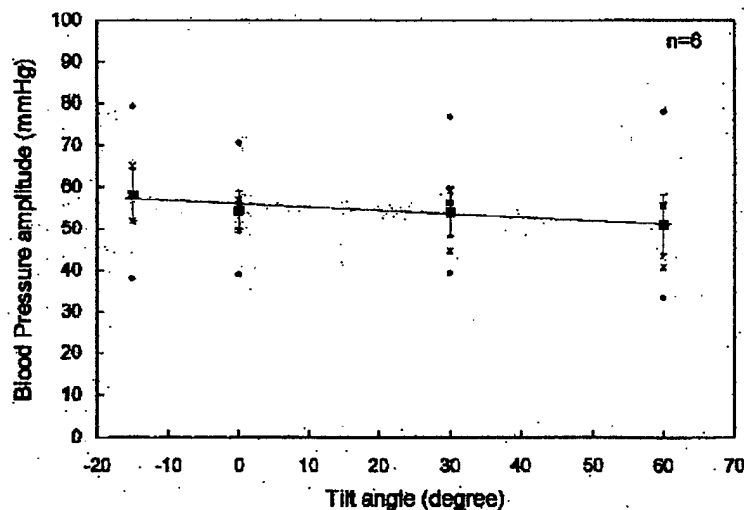


Figure 5 - Amplitude changes of arterial blood pressure pulsation during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

The amplitude of arterial blood pressure was not changed significantly as a function of the tilt angle ($r=0.188$, $p=0.378$; Figure 5). However, the amplitude of PPLL output significantly decreased as the angle of tilt was lowered ($r=0.535$, $p=0.007$; Figure 6). The PPLL output waveforms, which represent ICP pulsations, are primarily generated by arterial blood pressure waveforms (12,13), although venous pressure pulsation also has some effect on ICP pulsation. An increased amplitude of the arterial blood pressure could raise PPLL output amplitude, even if intracranial compliance remained constant. The modeling of intracranial compliance is thoroughly described in the annual report for Year 02 (March 1999).

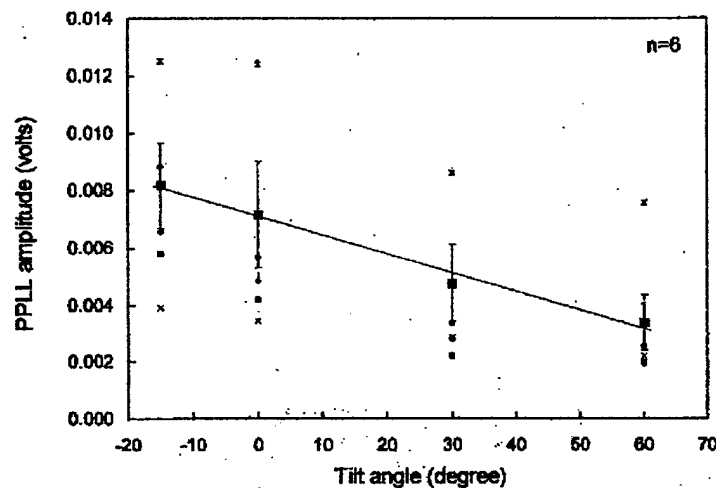


Figure 6 - Amplitude changes of ICP pulsation (PPLL output) during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

Year 03

Overview

Significant clinical experience was gained in Year 02 using normal volunteers in controlled experimental conditions. The data acquired during whole body tilt showed expected and reproducible trends, but also revealed unexpected challenges during data acquisition and results with much greater variability than those previously reported. Therefore, it became important to investigate ways to optimization the clinical measurement techniques before initiating additional studies at the bedside of patients with expected ICP anomalies. The procedures employed were analyzed and several areas were identified for further

investigation and optimization. These included both instrumentation variables and procedural techniques.

Instrumentation optimization

Transducer Assembly

The instrumentation is highly sensitive to changes in the acoustic pathlength. This characteristic is critical since the change in distance is related to ICP as demonstrated theoretically and in cadaver studies. Therefore it is imperative that the transducer is absolutely stationary so that changes in the pathlength do not occur due to transducer motion relative to the skull. Whole-body tilting required alterations in the position of the patient and alterations of the direction of the gravitation force experienced by the transducer and attached cable which could slightly alter its position. Therefore, we sought to reduce the size and weight of the transducer and increase flexibility of the cable.

It was determined that the size of the transducer influenced the signal strength and the time required for patient instrumentation. The smallest transducer (6.5mm) was difficult and time consuming to apply due to challenges in locating the reflection and in receiving a reduced signal amplitude. The largest transducer evaluated (25.4mm) provided the best signal quality and minimized the time required for locating the reflected pulse. Cable modifications were made to decrease weight and size and increase flexibility. These alterations considerably improved the transducer stability and the modified hardware was implemented in subsequent studies (Figure 7).

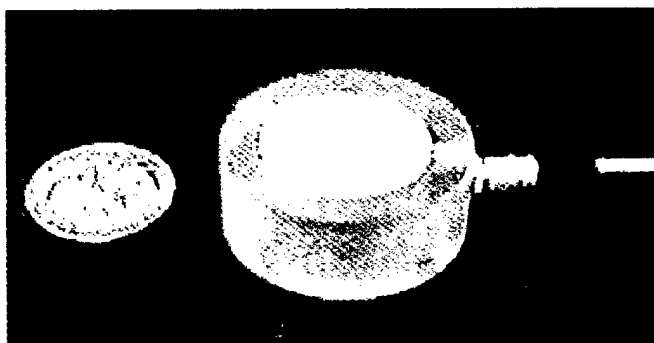


Figure 7 – Photograph of optimum transducer with improved cable assembly attached

Temporal Stability

The previous study also demonstrated that there was temporal dependence on the instrument output and measurement results. After the transducer was properly positioned, the resulting signal decreased in amplitude during the first minute. After approximately 60 seconds, the output signal reached steady state (Figure 8). This delay was identified as an intrinsic characteristic of the PPLL instrument, dependent upon the time constant in the circuit design. This information was important to identify further hardware improvements and optimize the measurement procedure further. The initial hardware improvements

degraded signal quality, so the original hardware was retained and subsequent measurements were performed at least 1 minute after patient instrumentation. Further modifications are anticipated and will be evaluated in effort to decrease the delay while maintaining signal quality. Such improvements would further decrease the time required for clinical measurements.

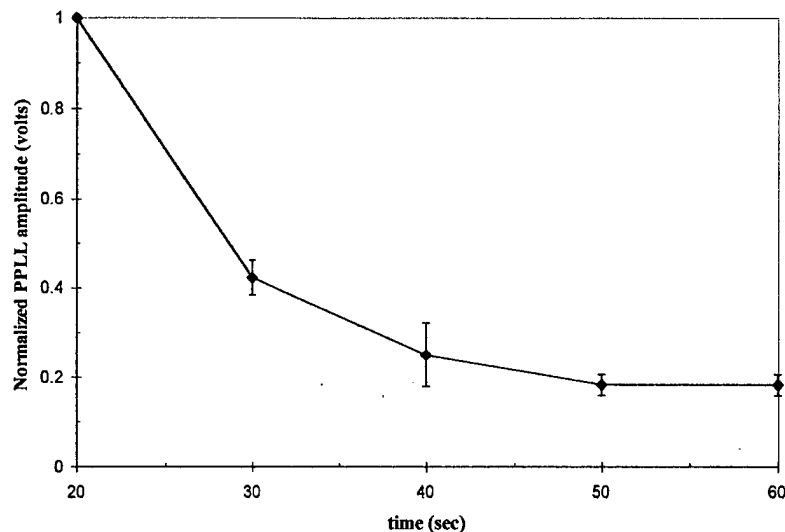


Figure 8 - Amplitude changes of PPLL output as a function of time. The inherent time delays in the instrument circuitry require approximately 60 seconds for the output to achieve steady state. Markers represent mean values from three measurements and vertical bars represent standard deviation of the mean

Calibration & Characterization

Calibration techniques were further developed to characterize the instrument output as a function of displacement. A portable in-vitro system, consisting of a water bath and computer controlled stepper motor (Compumotor, Parker Hannifin Corp., Rohnert Park, CA), was developed to replicate clinically relevant pathlengths, displacement amplitudes, and pulsation frequencies. The user controls each of the parameters through software (LabView, National Instruments, Austin, TX) and can therefore accurately characterize their influence on the instrument output signal. This system has both instrument (development, Q/A, testing) and clinical (displacement calibration, clinical simulation) applications. The output signal amplitude was proportional to clinically relevant displacement amplitudes from 1-10 μ m as measured at 60 bpm/1 Hz (Figure 9).

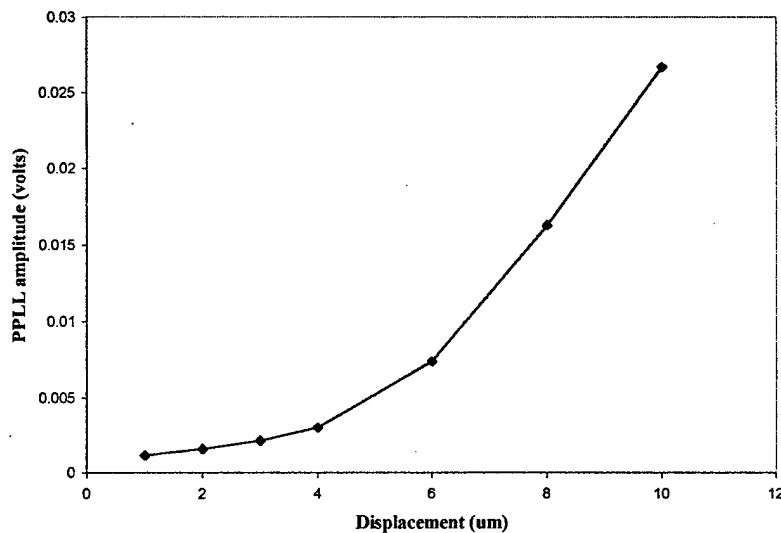


Figure 9 – In-vitro calibration technique depicting the relationship between the measured value and displacement of oscillations. The measurement is sensitive to displacements of a few microns.

The PPLL amplitude increased with increasing displacement and can be modeled as an exponential according to the following equation:

$$y = 0.0008 e^{0.3648x} \quad R^2 = 0.9942 \quad \text{equation 5}$$

where x = displacement (microns) and y = PPLL amplitude. These results and the application of this technique will allow us to accurately calibrate the instrument output as a function of displacement amplitude. It also provides a valuable in-vitro tool to characterize the response over a wide range of displacements and oscillation frequencies as well as compare instrumentation following modifications during future development and refinement.

Procedural Techniques

Location of Transducer

The placement of the transducer was studied to evaluate advantages and limitations of various mounting locations on the skull. The clinical condition and potential application for combat injuries may require transducer placement away from the trauma site or while head protection is worn. Furthermore, acoustic coupling may be influenced by skin lesions, hair, and other external features. Six different locations were selected at regular intervals (approximately one inch apart) between the ear and the forehead. The transducer was placed in each of the locations and secured with an elastic wrap and the ability to locate an adequate signal was qualitatively assessed.

Measurements were obtainable at only two of the six locations, the forehead and the temporal window (near the ear). Typically it was easiest to use the temporal window but

this depended somewhat on the skull geometry of the patient. The presence of roughly parallel bone structures seemed to simplify the procedure. Therefore, the shape of the patient's skull influenced the optimal measurement site and the temporal window was generally successful. The forehead placement (approximately between the eye brows) was more difficult, especially in those patients with posterior skull curvature, but a reasonable signal was obtainable. Future clinical applications will likely require transducer placement in one of these locations, which may be a limitation in certain scenarios but also demonstrates that measurements can be performed on patients wearing protective head gear provided the lower central forehead is exposed.

Reproducibility

Measurement reproducibility was evaluated by positioning the transducer at the temporal window location, securing it in place by wrapping with an elastic bandage, acquiring the measurement data, completely removing the instrumentation, and then repeating the procedure. The procedure was executed 10 times in each subject and the results compared.

Each attempt generated a successful measurement demonstrating the clinical reliability of the technique and instrumentation. The results showed variability on the order of 10%, which is less than the previously reported results for whole body tilting. This may be partially due to the low amplitude of the signal in normal, resting, upright patients which reduces the signal-to-noise ratio and represents values at the low end of the anticipated clinical range. The normal patient may talk, squint, cough, sneeze, and alter homeostasis which will influence this sensitive measurement. The operator may change the transducer position and coupling by altering mounting pressure and/or angle and influence the patient through instruction and interaction and instrument operation. Previous studies demonstrated that external compression influences the magnitude of displacement. Since the transducer is held in place with an elastic wrap, this may be a source of external compression that would depend on how tightly the operator applied the wrap. Modification of the mounting technique to reduce damping due to external compression and application of identical compressive forces would likely further reduce variability as well as facilitate clinical application. Thus a head-mounting device with controlled two point compression is expected to improve noninvasive ICP measurements significantly.

Key Research Accomplishments

- Experimental models that did not require the use of live subjects (animal or human) were successfully developed to simulate clinical conditions for instrument development, testing, characterization, and calibration.
- PPLL measurements were proportional to acoustic pathlength over a dynamic range that exceeds that expected in clinical applications.

- Signal amplitude and frequency characteristics of this noninvasive method correlated with those of currently-used invasive instruments.
- The technique was insensitive to temperature and therefore not significantly influenced by the acoustic properties of the soft tissues that are located between the reflecting surfaces.
- Pulsatile signal characteristics were detected and measured noninvasively and accurately reflected the pulsatile characteristics present in a cadaver model without the confounding effects of skin blood volume and pressure pulsations.
- Postural dependence was demonstrated in-vivo as predicted by the physiological fluid shifts induced by gravitational forces.
- Application of circumferential external forces reduced the magnitude of displacement as the applied force was increased.
- Hardware was evaluated and modified to optimize clinical application.
- Software was developed and improved to facilitate measurement and analysis.
- Calibration equipment and techniques were designed and used for development and clinical applications.
- Clinical procedures were evaluated and modifications identified to improve accuracy, reproducibility, and user-friendliness.

Reportable Outcomes

Publications for Period 1 Feb. 1997 to 31 Jan. 2000

(#1-7 attached in Year 01 and Year 02 annual reports, #8 attached to this report)

1. Ueno T, RE Ballard, WT Yost, and AR Hargens. Non-invasive measurement of intracranial pressure pulsation using ultrasound. *Aviation, Space and Environmental Medicine* 68:(7) 646(193), 1997.
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8. Ueno T, RE Ballard, L Rossetto, B Macias, JH Cantrell, WT Yost, and AR Hargens. Effects of whole body tilting on intracranial pressure dynamics. *Journal of Applied Physiology* (submitted)

List of Personnel whose Salary is Supported by this Effort:

Richard E. Ballard, M.S. – obtained M.S. under project
 Adnan Cutuk, B.S. – admitted to medical school under project
 Karen Hutchinson, A.A., R.N. – obtained R.N. under project
 Gita Murthy, Ph.D. – obtained Ph.D. under project
 Gregory C. Steinbach, Ph.D. – obtained postdoc support under project

Conclusion

The studies performed over the last three years partially validated and improved, the capabilities of this noninvasive technique for monitoring intracranial pressure (ICP). Significant advances were made in improving instrumentation and clinical implementation as well as identification of limitations and areas requiring further investigation. The results show that the technique can predictably monitor ICP dynamics, demonstrated both in-vitro and in-vivo, in real-time, with excellent sensitivity. The method is relatively inexpensive and noninvasive, providing significant advantages over existing techniques for research, military, and clinical applications. The current configuration could be utilized to monitor relative changes in ICP, but additional studies and instrument modifications would improve and expand its utility. The instrumentation would benefit from design modifications to reduce the internal time constant to allow a more rapid response upon initial placement of the transducer on the patient. More importantly, design and development of a transducer headset would expedite the placement and allow better control over contact force, minimize circumferential forces, and allow better signal

acquisition. Additional clinical studies are necessary to establish further the relationship between blood pressure, ICP, and this measurement of variations in cranial dimension. The potential applications are enormous and even the current capability to monitor relative ICP changes provides for the ability to assess improvement or degradation status of a patient. This information may prove valuable in patient management by providing diagnostic feedback to the clinician indicating the need for continued monitoring, referral for further intervention, monitoring the effect of treatments (e.g. hypertonic infusions), and allowing resumption of normal activity/duty.

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APPENDIX

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

$$n\Delta\lambda = \Delta l \quad (\Delta\lambda : \text{changes in wavelength, } \Delta l : \text{changes in distance})$$

where $n = 2l/\lambda$ (l : initial distance between a transducer and a target, λ : initial wavelength).

Therefore,
$$\frac{\Delta\lambda}{\lambda} = \frac{\Delta l}{l}$$

Also,
$$\Delta\lambda = \frac{\partial\lambda}{\partial v} \Delta v + \frac{\partial\lambda}{\partial f} \Delta f$$
 where Δv is changes in ultrasound velocity. and $f = v/\lambda$.

Solving these equations, we obtain
$$\frac{\Delta f}{f} = \frac{\Delta v}{v} - \frac{\Delta l}{l}$$

If changes in sound velocity are negligible, the above equation is finally expressed as:

$$\frac{\Delta f}{f} = -\frac{\Delta l}{l}$$

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Effects of Whole Body Tilting on Intracranial Pressure Dynamics

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SUMMARY

This study was designed to investigate effects of whole body head-down tilting on intracranial compliance and pressure in six healthy volunteers (two male and four female) by using a noninvasive ultrasonic device. Subjects were randomly tilted up or down sequentially at 60°, 30° head-up, and supine, and 15° head-down position for one minute at each angle. We measured arterial blood pressure with a finger pressure cuff, and changes in intracranial distance with an ultrasonic device. The device measures skull movement on the order of μm which is highly correlated with intracranial pressure variations due to cerebral arterial pulsation. The amplitudes of arterial blood pressure and those of intracranial pressure associated with one cardiac cycle were inversely correlated with the angle of tilt. The ratio of pulsation amplitudes for intracranial pressure over arterial blood pressure also showed a significant increase as the angle of head-down tilt was increased. Thus, postural changes alter intracranial compliance in healthy volunteers and intracranial volume-buffering capacity is reduced in head-down position. (162 words)

INTRODUCTION

Intracranial pressure (ICP) dynamics are important for understanding adjustments to altered gravity. It is speculated that ICP is elevated during microgravity due to a fluid shift to the head³². Because there are no valves in veins above the neck so as to facilitate blood return to the heart¹⁴, blood easily stagnates and accumulates in the veins of the head and neck during space flight. Increased blood volume in the head could elevate intracranial pressure because the brain is surrounded with relatively rigid skull. As widely observed in clinical settings, elevated ICP causes headache, nausea and projectile vomiting¹⁸, which are similar to symptoms of space adaptation syndrome²⁶. Elevated ICP may also comprise cerebral circulation. ICP dynamics are therefore important for understanding physiological adaptation during exposure to microgravity.

However, there are no experimental results to support the hypothesis that ICP is actually altered during microgravity exposure, primarily due to the invasiveness of currently-available techniques. By using invasive techniques, several ground-based experiments demonstrate that ICP increases during exposure to head-down tilt^{19,20,29}, which is commonly used for simulation of microgravity. Although these previous data support the suggestion that ICP is elevated during space flight, the data were obtained in patients or animals. It is still unknown whether or not ICP in healthy volunteers actually changes in microgravity or even to postural changes on Earth.

We have developed and refined an ultrasonic device which can measure changes in intracranial distance noninvasively^{7,30}. Although the skull is assumed to be rigid, many investigators report that the skull moves on the order of μm in association with the arterial pulse and consequent ICP pulsation^{2,5,11,16,22,27}. Our ultrasonic device records ICP waveforms noninvasively from skull movements. Measurements by our ultrasonic device correlate well ($R^2 = 0.80$) with invasively measured ICP in cadavers³⁰.

This ultrasonic technique enables us to evaluate ICP dynamics noninvasively by analyzing pulsatile components of ICP waveforms. Amplitudes of pulsatile components of ICP yield information on intracranial compliance, representing the magnitude of ICP change with a change in volume of any intracranial component (brain, blood or cerebrospinal fluid)²¹. Clinically, intracranial compliance is important to monitor because

it represents the volume-buffering capacity of the intracranial tissues and fluid. In addition, because the intracranial volume-pressure curve is generally exponential, an inverse relationship exists between intracranial compliance and pressure²¹. Thus, changes in mean ICP level can also be estimated from pulsatile components of ICP waveforms.

The present study was therefore designed to investigate whole body tilting effects on ICP dynamics, especially intracranial compliance, using our noninvasive technique. We hypothesized that head-down tilt reduces intracranial compliance due to a blood shift to the head followed by elevation of ICP.

METHODS

PROCEDURE

The protocol of this study was approved by NASA Ames Human Research Institutional Review Board. Six healthy volunteers (two males and four females: age with mean \pm SD of 24 \pm 4 years old, height 168 \pm 10 cm, and weight 66 \pm 13 kg) participated in this study, after giving informed written consent. To minimize accumulative effects caused by tilting, the subjects were randomly tilted up or down sequentially at 60°, 30° head-up, supine (0°), and 15° head-down position for one minute at each angle.

MEASUREMENTS

Arterial blood pressure: Arterial blood pressure and heart rate were monitored with an inflatable wrap-on finger pressure cuff (Finapres Model 2300, Ohmeda, Englewood, CO). An infrared plethysmograph mounted on the inside of the pressure cuff detected changes in the arterial blood volume³³. A very fast pneumatic valve varied finger cuff pressure to oppose the initial changes in the arterial blood volume. In principle, the cuff never occluded the artery. Accordingly, the cuff pressure followed intra-arterial pressure changes continuously. A finger, a measurement point, was placed at the heart level throughout the procedure. According to previous studies, blood pressure measured with Finapres correlates well with blood pressure measured with a standard technique during postural changes²⁵.

Cranial distance: ICP waveforms were monitored noninvasively using a modified pulse phase locked loop (PPLL) technique^{7,30,35}, which measured slight changes in transcranial distance. Thus, the PPLL technique measured ICP waveforms in arbitrary units. In the typical operation of the PPLL, the instrument transmits a 500 kHz ultrasonic tone burst through the cranium via a transducer placed on the head. The ultrasonic wave passes through the cranial cavity, reflects off the inner surface of the opposite side of the skull, and is received by the same transducer (Figure 1). The instrument compares the phase of emitted and received ultrasonic waves and alters the frequency of the next stimulus to maintain a 90° phase difference between the output of the device and the received signal. This repetition takes place at intervals of approximately 0.5 ms.

Changes in wavelength after the frequency shift which maintains a 90° phase difference between the output of the device and the received signal can be expressed as:

$$n\Delta\lambda = \Delta l \quad (\Delta\lambda: \text{changes in wavelength, } \Delta l: \text{changes in distance})$$

where (l : initial distance between a transducer and a target, λ : initial wavelength).

Therefore, $\frac{\Delta\lambda}{\lambda} = \frac{\Delta l}{l}$ because $n\lambda = l$. Also, $\Delta\lambda = \frac{\partial\lambda}{\partial v}\Delta v + \frac{\partial\lambda}{\partial f}\Delta f$ where Δv is change in ultrasound velocity and $f = v/\lambda$.

$$\text{Solving these equations, we obtain } \frac{\Delta f}{f} = \frac{\Delta v}{v} - \frac{\Delta l}{l}.$$

Changes in sound velocity are negligible during a cardiac cycle. Therefore, the above equation is finally expressed as

$$\frac{\Delta f}{f} = -\frac{\Delta l}{l}$$

Although the ultrasonic frequency is altered every 0.5 ms by the PLL circuit, the number of the ultrasonic frequency can be transferred to a recording system 3-5 times per second. This sampling rate is not enough to analyze pulsatile components associated with a cardiac cycle. Recently, we modified a PLL circuit so as to record pulsatile components of the cranial distance in higher sampling rates. The modified PLL circuit integrates error signals of the phase shift from normal 90° phase difference while the ultrasonic frequency is being altered. The integrated error signal, which is obtained in the units of voltages, theoretically correlates with altered path length (Δl) relatively.

Furthermore, we performed signal averaging using the QRS complex of the electrocardiogram as a trigger. A data stream recorded over 30 seconds is fragmented using the QRS complex. Then, the fragmented data are simply summed up and divided by the number of a cardiac cycle. Although the length of each fragmented data is different from data to data due to the variability of a cardiac cycle, this variability is not taken into account. By averaging data across several cardiac cycles using the QRS

complex, superimposed noises which are not associated with a cardiac cycle are canceled, and waveforms associated with arterial pulsation can be shown more clearly.

STATISTICAL ANALYSIS

Amplitudes of ABP and PPLL output waveforms during one cardiac cycle at each angle of tilt were calculated from the data averaged using the QRS complex. The amplitude was defined as differences between maximum and minimum values during one cardiac cycle. These amplitude data were used for statistical analysis.

For statistical analysis, linear regression analysis was performed to determine the effects of tilt angles on amplitudes. Statistical significance is set to $p < 0.05$.

RESULTS

Figure 2 shows typical averaged waveforms of ABP and PPLL output in one subject. The ABP waveform peak does not coincide with that of PPLL output waveforms. This phase difference occurs because the distance from the heart to a finger is longer than from the heart to the head. Also, a filtering circuit incorporated in the PPLL circuitry causes a phase delay. The phase delay does not affect waveform analysis in the present study because we focus on amplitude of each waveform.

Linear regression analysis revealed the amplitude of arterial blood pressure were not changed significantly as a function of the tilt angle ($r=0.188$, $p=0.378$; Figure 3). However, the amplitude of PPLL output significantly decreased as the angle of tilt was lowered ($r=0.535$, $p=0.007$; Figure 4). The PPLL output waveforms, which represent ICP pulsations, are primarily generated by arterial blood pressure waveforms^{3,15}, although venous pressure pulsation also has some effect on ICP pulsation. An increased amplitude of the arterial blood pressure could increase the amplitude of the PPLL output, even if intracranial compliance remains constant. However, as shown in Figure 3, overall results of the arterial blood pressure did not show significant changes as a function of the tilt angle. On the other hand, it is possible that the observed change in the PPLL output at each angle of tilt was affected by that in arterial blood pressure.

Simply, there are two steps in the transmission of arterial blood pressure pulsation to ICP pulsation. In the first step, arterial pressure pulsation (ΔABP) causes arterial volume pulsation (ΔABV). Arterial volume increases when arterial pressure increases, and arterial volume decreases when arterial pressure decreases. In the second step, arterial volume pulsation (ΔABV) generates ICP pulsation (ΔICP). Because the intracranial space is surrounded by a relatively rigid skull, an increase in arterial volume causes an increase in ICP pulsation, On the other hand, a decrease in arterial volume causes a decrease in ICP pulsation.

Generally, compliance is defined as a ratio of change in volume over the corresponding change in pressure. Therefore, compliance of artery (C_{artery}) and intracranial space ($C_{intracranial}$) are expressed as:

$$C_{artery} = \frac{\Delta ABV}{\Delta ABP} \dots\dots(1) \quad C_{intracranial} = \frac{\Delta ABV}{\Delta ICP} \dots\dots(2)$$

From the equations (1) and (2), we obtain

$$\frac{C_{\text{intracranial}}}{C_{\text{artery}}} = \frac{\Delta \text{ABP}}{\Delta \text{ICP}} \therefore C_{\text{intracranial}} = C_{\text{artery}} \frac{\Delta \text{ICP}}{\Delta \text{ABP}} \dots\dots(3)$$

Consequently, we calculated ratios of pulsation amplitudes for PPLL output over arterial blood pressure, which may be more directly associated with intracranial pressure compliance. The ratios of pulsation amplitudes for PPLL output over arterial blood pressure significantly decreased as the angle of tilt was lowered ($r=0.409$, $p=0.047$; Figure 5).

DISCUSSION

The ultrasonic technique (PPLL) utilized in this study was originally developed by Yost and Cantrell at NASA Langley Research Center, and has been refined in collaboration with Space Physiology Lab at NASA Ames Research Center. PPLL outputs theoretically represent skull movement, namely cranial diameter pulsation. According to our previous cadaver study³⁰, where ICP pulsation is manually generated, the amplitude of cranial diameter pulsation at each pulsatile cycle is linearly correlated with ICP pulsation amplitude. Additionally, a preliminary clinical study at Stanford Medical Center in patients whose ICP was monitored by the standard invasive technique showed good correlation between the invasive and noninvasive ICP measurement techniques during a short period (10-15 minutes)³¹. Thus, our technique provides reliable data in terms of the pulsatile component of ICP when measurements are conducted during relatively short periods such as in the present study. Because our technique is very sensitive to distance changes, further studies are necessary to apply this technique for monitoring ICP over larger time periods.

In the present study, a concern may be raised that postural changes caused erroneous variability and false-positive changes in the PPLL amplitude. However, we believe that effects of such motion artifacts were cancelled out by randomizing the order of tilt angles. Accordingly, we conclude that the observed changes in the amplitudes of the PPLL output represent those in the amplitudes of ICP pulsation.

ICP pulsation associated with a cardiac cycle is primarily generated by arterial blood pressure pulsation^{3,15}, although venous pressure pulsation also has some effect on ICP pulsation. As discussed earlier, intracranial compliance is expressed as;

$$C_{\text{intracranial}} = C_{\text{artery}} \frac{\Delta \text{ICP}}{\Delta \text{ABP}} \dots\dots(4)$$

where $C_{\text{intracranial}}$, C_{artery} , ΔABP , and ΔICP are intracranial compliance, compliance of artery, arterial pressure pulsation, and ICP pulsation, respectively.

In the present study, we did not measure compliance of artery in the brain. Based upon previous reports^{6, 23, 34}, however, it seems reasonable to assume that compliance of artery was changed in the following manner during exposure to whole body tilting.

Elasticity of an arterial wall decreases as the wall is extended, although an arterial wall is assumed to be elastic. Thus, the relationship between arterial volume and pressure is expressed as an exponential curve²³ (Figure 6). Although mean arterial pressure at the heart level is not shown in the results, mean arterial pressure at the head level, not heart level, is obviously much higher in a head-down position than in a head-up position, due to less hydrostatic gravitational pressure difference between the heart and head level. Note that theoretical amplitudes are not affected by changes in hydrostatic pressure because hydrostatic pressure has the same effect on systolic and diastolic pressure. This higher mean arterial pressure at the head level shifts the stable point from #1 to #2 in Figure 6 when a subject is tilted down. Accordingly, the amplitude of arterial blood volume at the head level, ΔABV , should be decreased in a head down position. In addition, it is likely that cerebral autoregulation is triggered as the angle of head-down tilt is increased as previously reported^{6,34}. In other words, cerebrovascular tonus increases to compensate against elevation of increased arterial blood pressure within the head. Therefore, the pressure-volume curve of the artery shifts toward the left, resulting in a shift of a stable point from #2 to #3 in Figure 6. This shift causes further decrease in ΔABV (Figure 6). Thus, taken together, C_{artery} decreases in the head-down position from the equation (1).

In the results, a ratio of PPLL output over arterial pressure amplitudes, $\frac{\Delta ICP}{\Delta ABP}$, increases as the angle of head-down tilt increases. Consequently, in the equation (4), $C_{intracranial}$ decreases as the angle of head-down tilt increases. Because compliance is defined as the ratio of volume change to the corresponding pressure change, the decrease in $C_{intracranial}$ suggests that the volume-buffering capacity of the intracranial system is reduced in a head-down position.

Because the intracranial space is surrounded with a relatively rigid skull, the relationship between intracranial arterial volume and pressure and intracranial extravascular volume and pressure are both exponential. This non-linear relationship between intracranial volume and pressure is originally reported by Marmarou²¹, and many clinical observations support the existence of this relationship^{4,8,9}, which is depicted in Figure 7. As defined in the equation (2), $C_{intracranial}$ is an inverse of the slope

in the pressure-volume curve. Thus, a decrease in $C_{intracranial}$ indicates that a stable point shifts from the point #1 to #2 when a subject is tilted down. Although our technique does not provide mean ICP directly, the shift from the point #1 to #2 in Figure 7 indicates an increase in mean ICP. Several studies^{10,17,28} report that ICP decreases in a head-up position in patients with head trauma or other intracranial diseases. Also, it has been reported that ICP increases at a head-down position in the monkey¹⁹, cat²⁰, and rat²⁹. However, it has not been reported how ICP actually responds to large changes of posture in normal healthy humans. This is simply due to the invasiveness of currently available techniques. The present study may be the first report to suggest that postural changes alter intracranial compliance and pressure in normal healthy subjects.

In the field of space medicine, head-down tilt has been used as a method to simulate effects of microgravity on cardiovascular circulation. It may be controversial whether or not head-down tilt also simulates effects of microgravity on ICP. However, placing a subject in a head-down position mimics facial puffiness that is usually observed during space flight better than supine posture²⁴. Thus, we expect that head-down tilt produces a similar hydrostatic pressure effect on the cerebrovascular and cerebrospinal fluid systems as exposure to microgravity. In the present study, intracranial compliance is reduced as the angle of tilt is lowered. Accordingly, we do conclude that postural changes significantly alter intracranial compliance and pressure in normal volunteers. Although we cannot extrapolate our results directly to microgravity exposure, the present study therefore encourages us to do further studies using our ultrasonic technique to clarify effects of microgravity on ICP. Our technique has the feasibility of measurements during space flight because of its compactness and minimal risk to the test subject.

CONCLUSIONS

Our noninvasive ultrasonic technique reveals that whole-body head-down tilting decreases intracranial compliance and increases intracranial pressure in normal healthy volunteers. We also suggest that intracranial volume-buffering capacity is reduced in head-down position.

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FIGURE LEGENDS

Figure 1 Principle of the PPLL. When a reflecting point moves (A), a phase difference occurs between an emitted and a received ultrasonic wave (B). The phase difference activates a voltage-oscillator in the PPLL circuit, resulting in generating an error signal. This error signal exists until the PPLL circuit alters the ultrasonic frequency of the next stimulus so as to correct a phase shift (C). The PPLL analog output is given by integrating the error signal, which represents changes in distance.

Figure 2 Typical waveforms in arterial blood pressure and PPLL output are shown as solid and dash lines, respectively. Because arterial blood pressure is measured at finger, a phase difference exists between two waveforms.

Figure 3 Changes in the amplitudes of arterial blood pressure pulsation during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

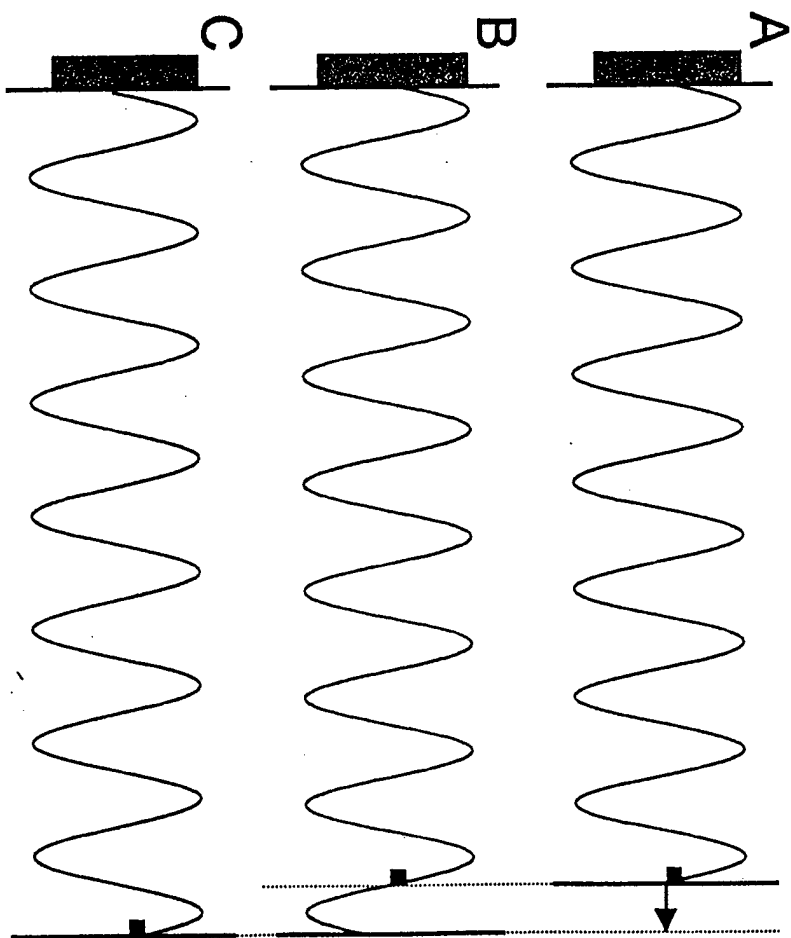
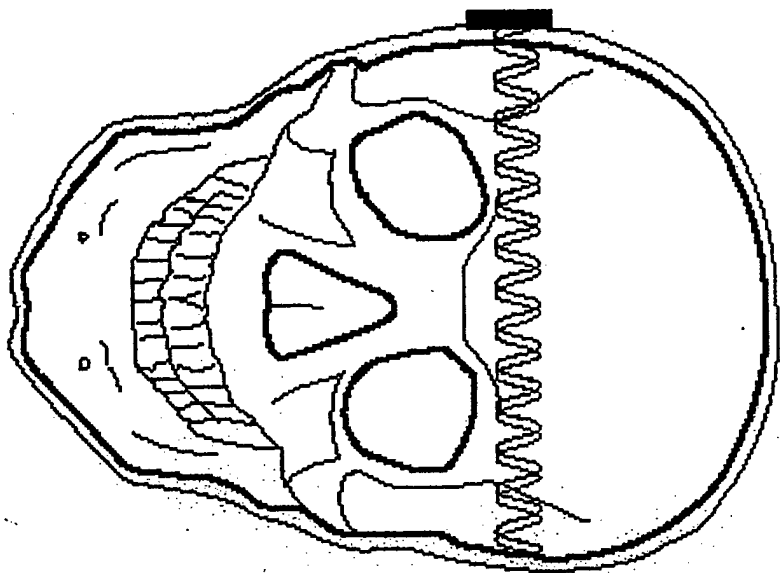
Figure 4 Changes in the amplitudes of ICP pulsation during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

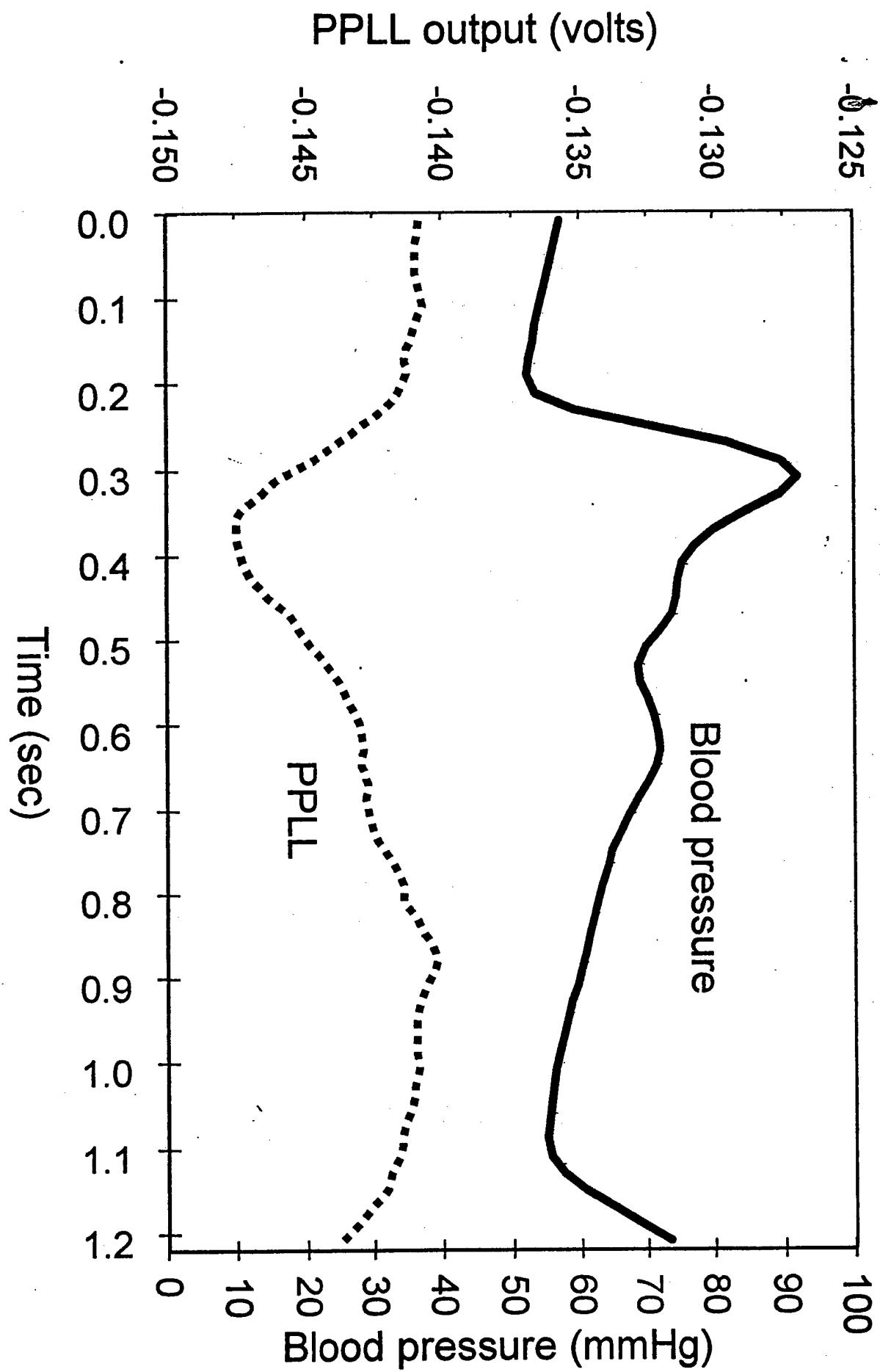
Figure 5 Changes in the ratio of the ICP amplitudes to the arterial pressure amplitudes during whole body tilting. Small symbols represent individual data, and large squares represent mean values in six subjects. Vertical bars represent standard errors of the mean.

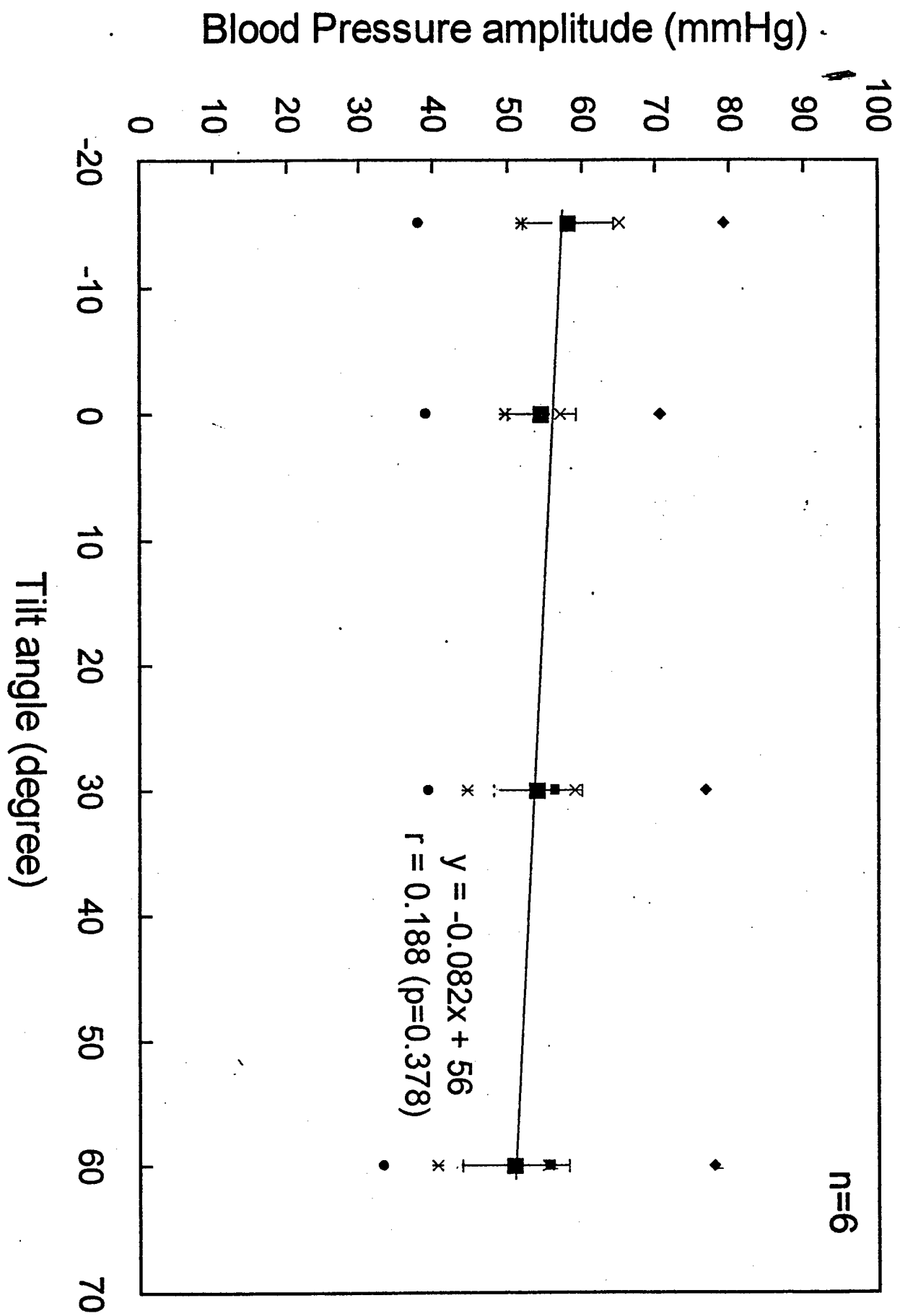
Figure 6 Characteristics of the relationship between arterial blood pressure and volume. The horizontal axis represents volume in cerebral arteries. The vertical axis represents arterial blood pressure. A solid exponential curve shows the pressure-volume relationship when vascular tonus is normal, while a dashed curve shows the relationship when vascular tonus is increased due to autoregulatory response.

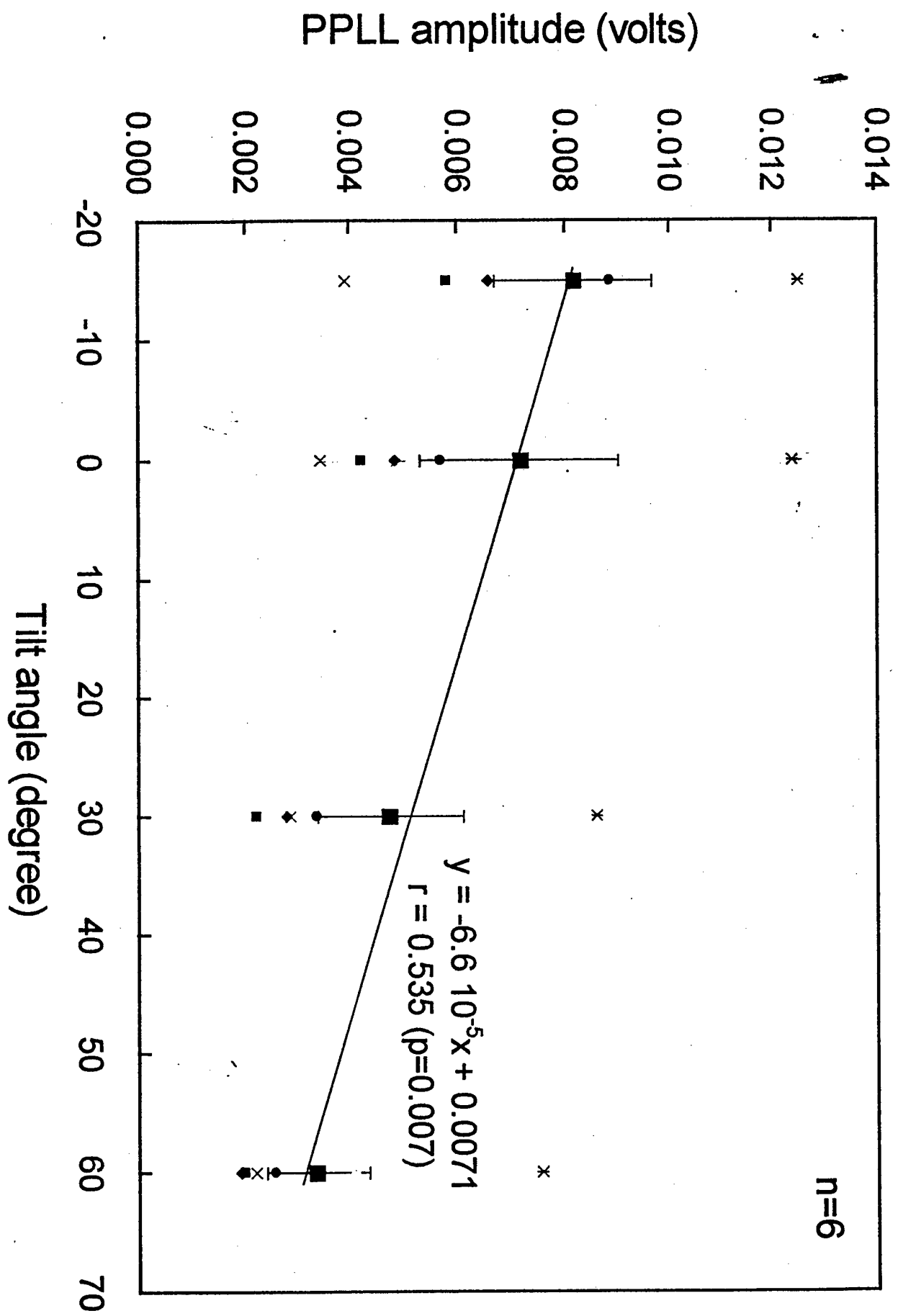
Figure 7 Characteristics of the relationship between intracranial pressure and volume are originally described by Marmarou²¹. The horizontal axis represents volume

of all intracranial components (brain tissue, blood, and cerebrospinal fluid). The vertical axis represents ICP.









intracranial pressure

amplitude of intracranial
pressure pulsation

ΔICP_2

ΔICP_1

#1

#2

ΔABV

ΔABV

intracranial volume

amplitude of arterial volume pulsation

